ENERGY LANDSCAPES AND FOLDING KINETICS OF PAIRWISE INTERACTING RNAS

Stefan Badelt[1], Christoph Flamm[2], Ivo L. Hofacker[2]

(1) DNA and Natural Algorithms Group,
California Institute of Technology

(2) Theoretical Biochemistry Group (tbi),
University of Vienna

Munich, Sept, 5th, 2016

OUTLINE

RNA modeling and RNA energy landscapes

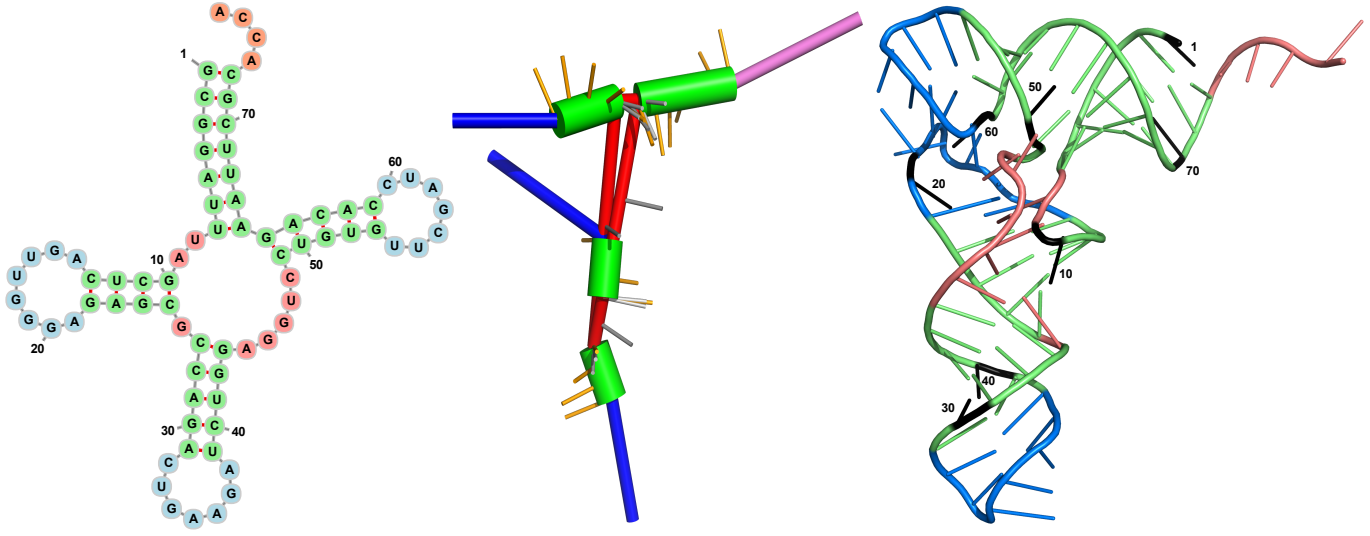
Coarse grained RNA folding kinetics

Folding kinetics of RNA-RNA interactions

Analysis of toehold-mediated interactions

RNA STRUCTURE

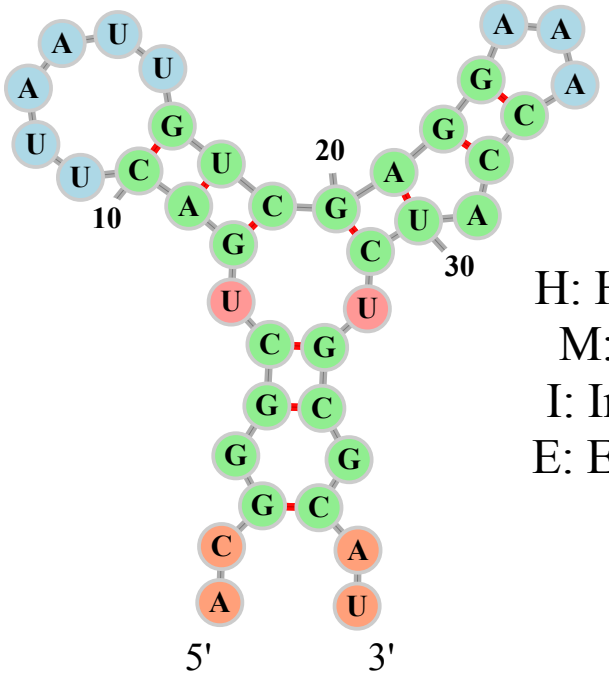
GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA



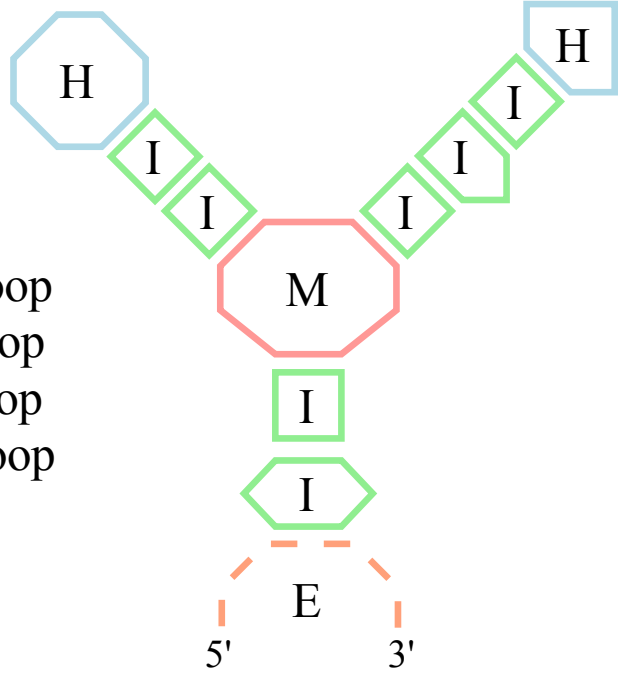
A secondary structure is a list of base pairs, where:

- A base may participate in at most one base pair
- Base pairs must not cross (no pseudoknots)
- Only isosteric base-pairs (GC, AU, GU) are allowed.

THE NEAREST NEIGHBOR ENERGY MODEL



H: Hairpin loop
M: Multi loop
I: Interior loop
E: Exterior loop



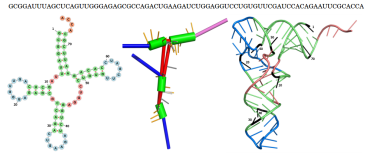
$$E(s) = \sum_{l \in s} e(l)$$

ENERGY LANDSCAPES

An energy landscape is defined by

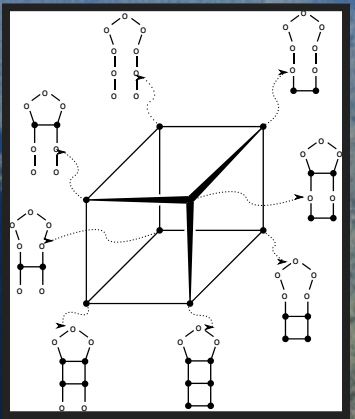
- Conformation space $s \in \Omega$
- Neighborhood relation [Move set] $M(s)$
- Energy function $E(s)$

RNA STRUCTURE REPRESENTATION

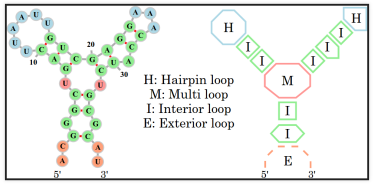


A secondary structure is a list of base pairs, where:

- A base may participate in at most one base pair
- Base pairs must not cross (no pseudoknots)
- Only isosteric base-pairs (GC, AU, GU) are allowed.

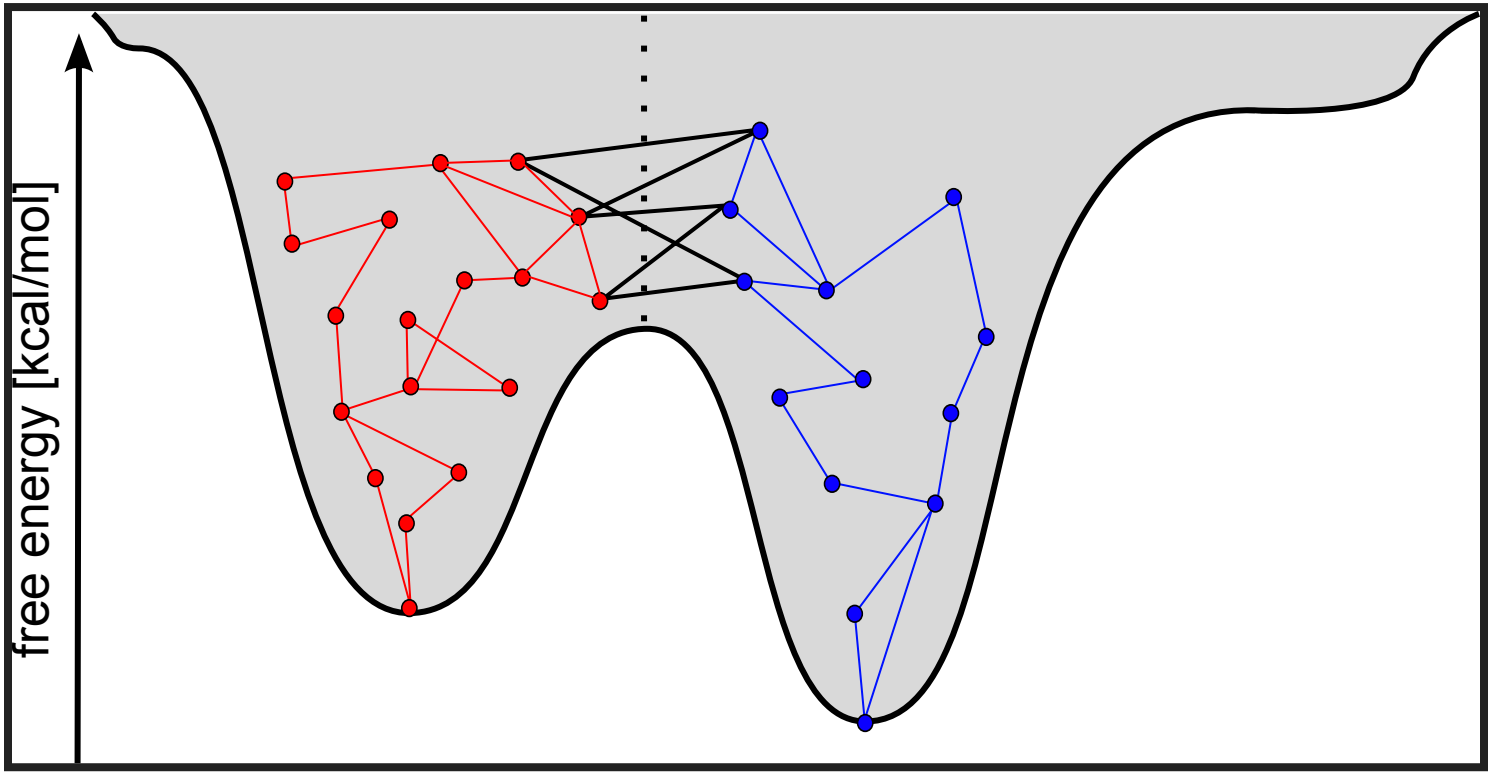


THE NEAREST NEIGHBOR ENERGY MODEL



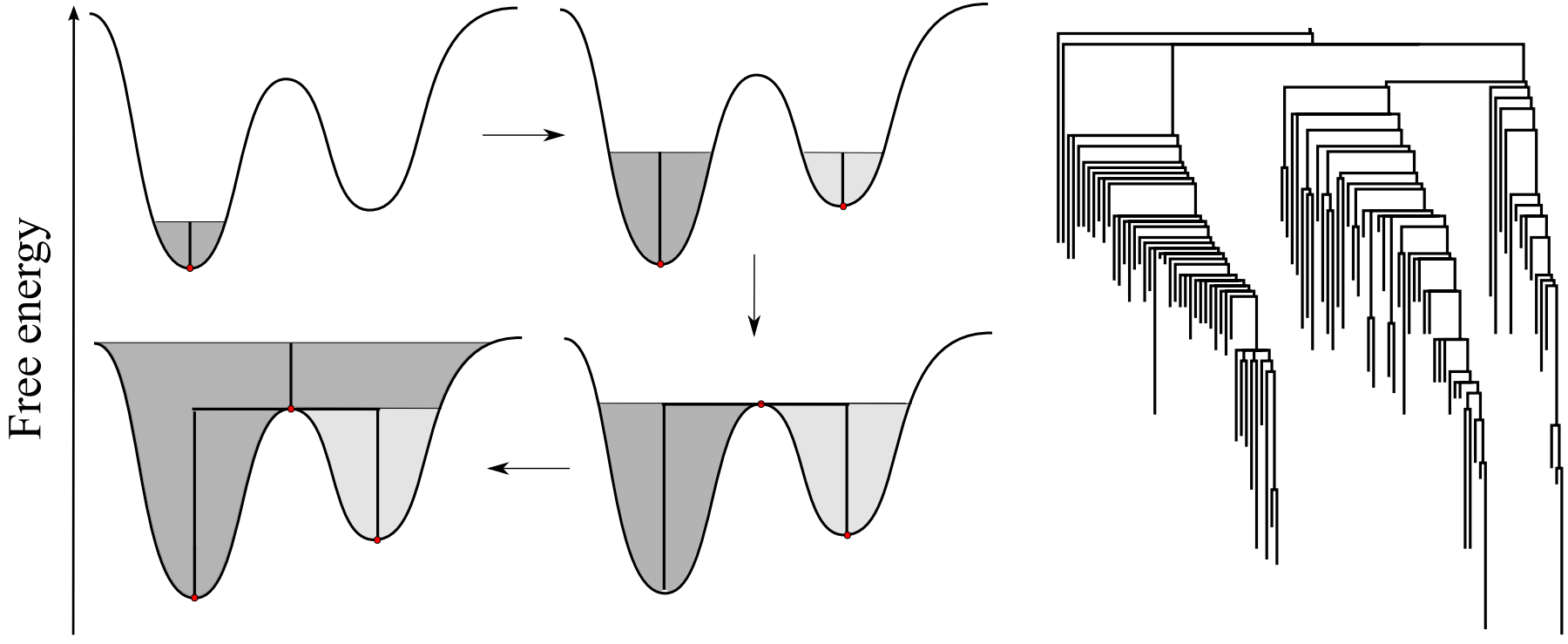
$$E(s) = \sum_{l \in s} e(l)$$

ENERGY LANDSCAPES



$$Z = \sum_{s \in \Omega} e^{\frac{-E(s)}{kT}} \qquad G = -kT \ln Z \qquad P(s) = \frac{e^{-E(s)/kT}}{Z}$$

ENERGY LANDSCAPES



Christoph Flamm, Walter Fontana, Ivo L Hofacker, and Peter Schuster
RNA folding at elementary step resolution. RNA, 6:325–338, 2000.

Michael T. Wolfinger, Andreas Svrcek-Seiler, Christoph Flamm, Ivo L. Hofacker, and Peter F. Stadler.
Efficient computation of RNA folding dynamics. Journal of Physics A: Mathematical and General, 37:4731–4741, 2004.

KINETICS

Calculate transition rates from energy barriers

$$\Delta G^{\ddagger} = E(s_j) - E(s_i)$$

$$k_{ij} = \begin{cases} k_0 & \text{if } \Delta G^{\ddagger} \leq 0 \\ k_0 e^{-\frac{\Delta G^{\ddagger}}{RT}} & \text{otherwise} \end{cases}$$

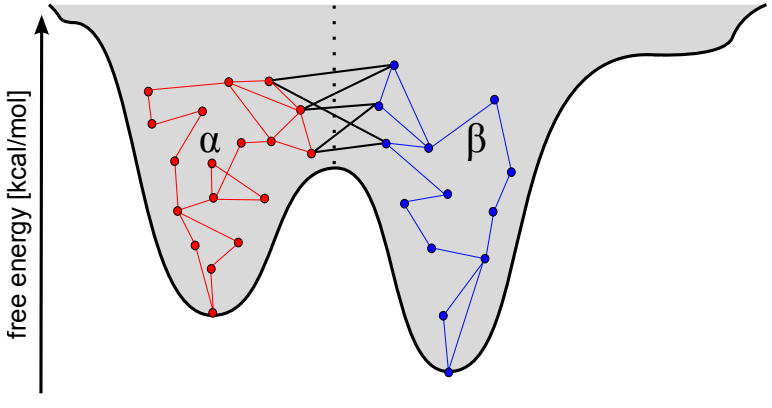
... where k_0 is a constant to relate folding to wall-clock time

N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, and E. Teller. **Equation of state calculations by fast computing machines.** The Journal of Chemical Physics, 21(6):1087–1092, 1953.

THE CHEMICAL MASTER EQUATION

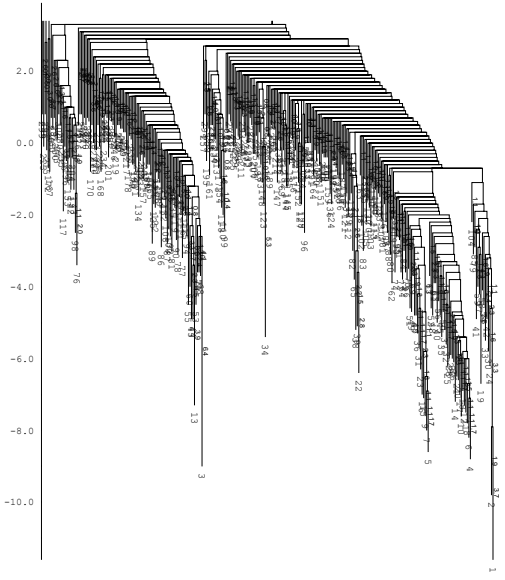
$$\frac{dP_i(t)}{dt} = \sum_{i \neq j} (P_j(t)k_{ji} - P_i(t)k_{ij})$$

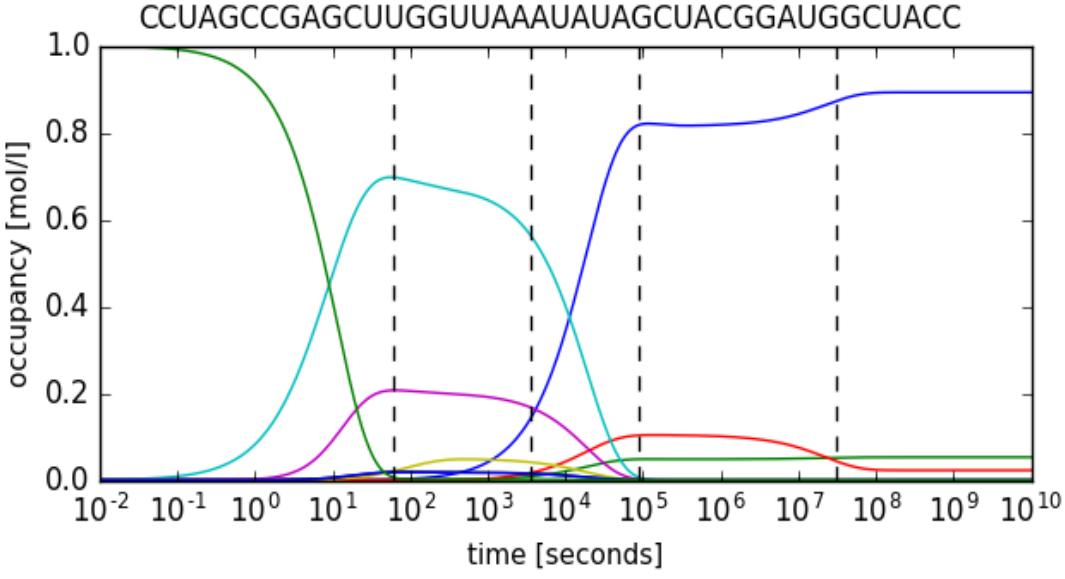
... together with the rates of gradient basin transitions ...



$$k_{\alpha\beta} = \sum_{i \in \alpha} \sum_{j \in \beta} P(i|\alpha)k_{ij}$$

… can be solved for 60-80 nucleotides sequence length

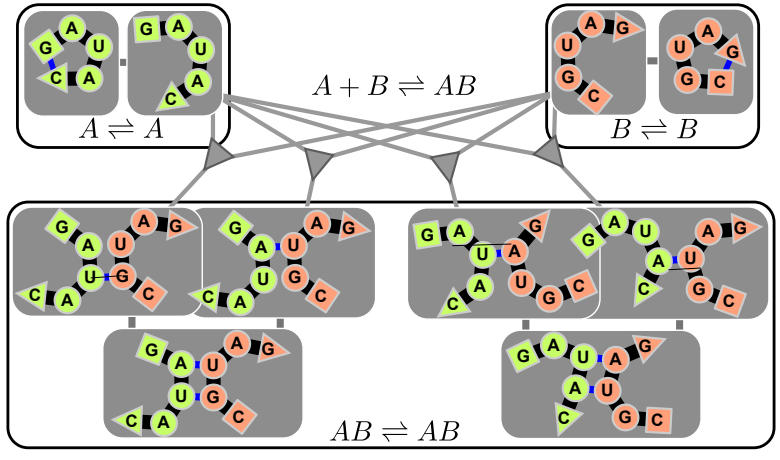




RNA-RNA INTERACTIONS

are concentration dependent...

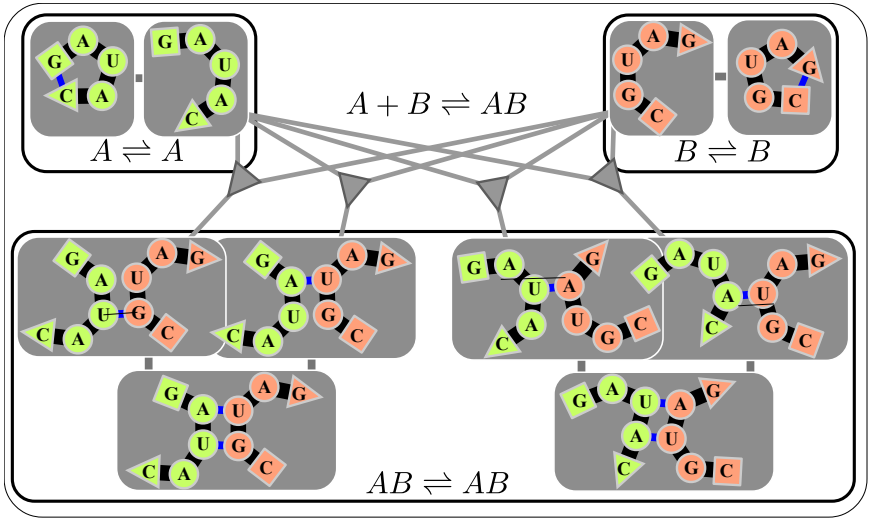
$$\frac{[AB]}{[A][B]} = K_{AB} = \frac{Z'_{AB}}{Z_A Z_B}$$

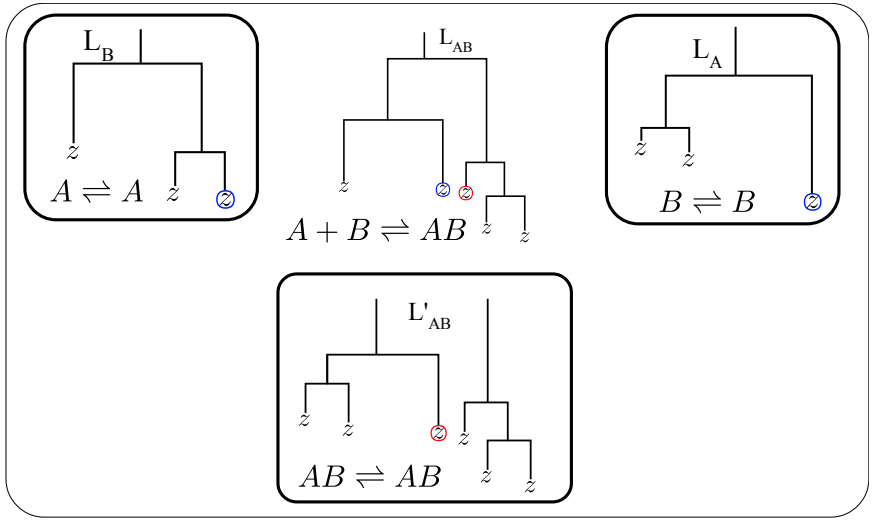


RNA-RNA INTERACTIONS

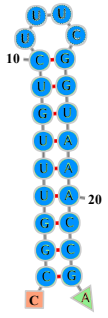
are concentration dependent...

$$\frac{[AB]}{[A][B]} = K_{AB} = \frac{Z'_{AB}}{Z_A Z_B}$$

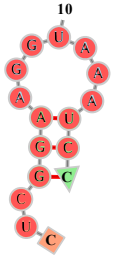




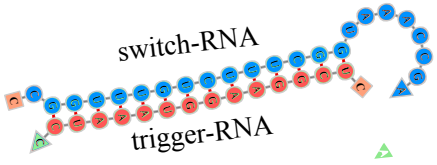
DESIGN SEQUENCE PAIRS



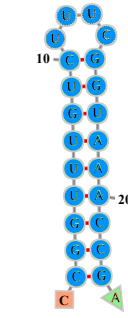
switch-RNA



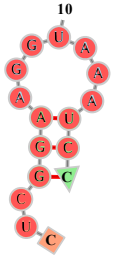
trigger-RNA



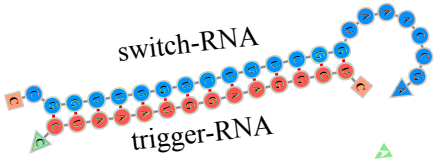
DESIGN SEQUENCE PAIRS

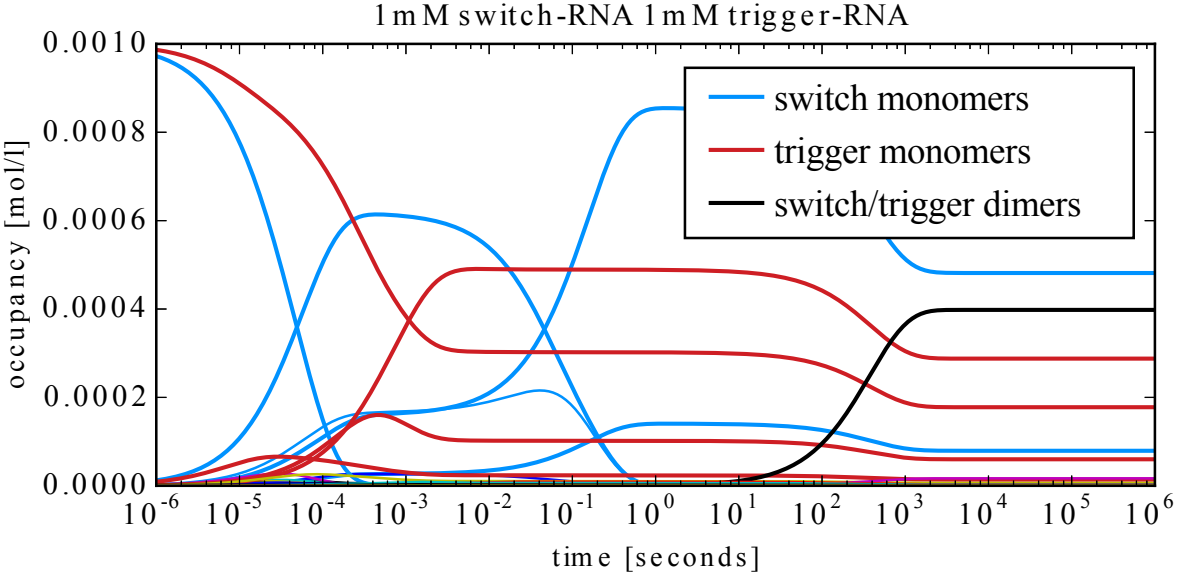


switch-RNA

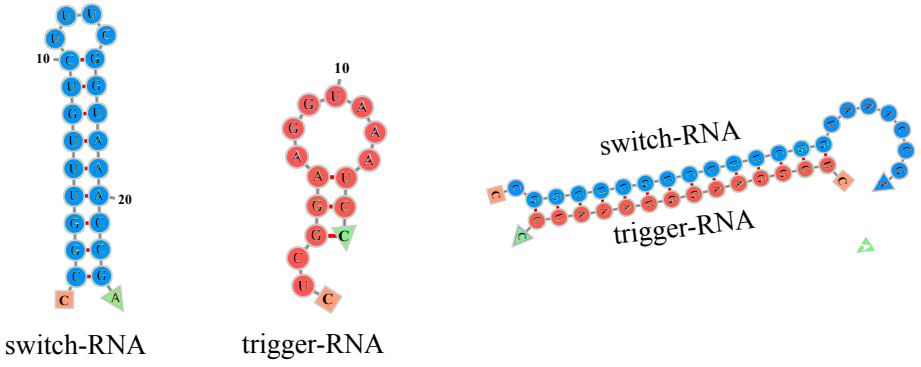


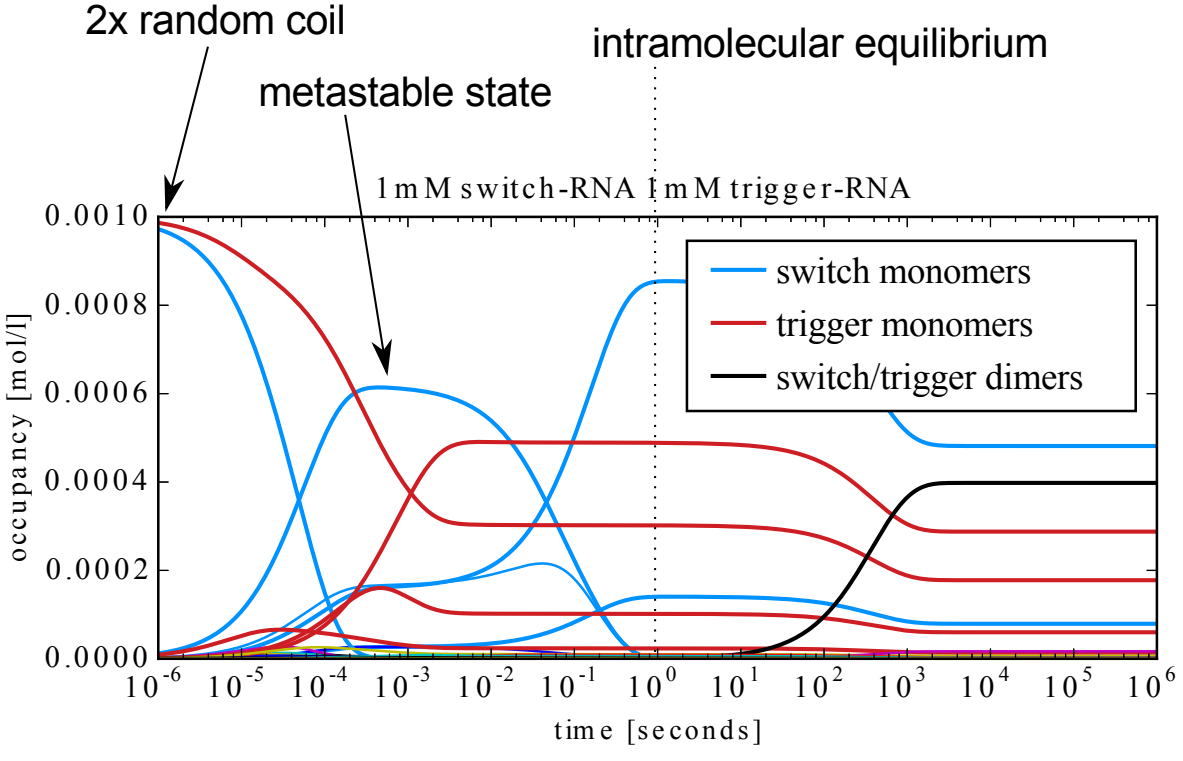
trigger-RNA



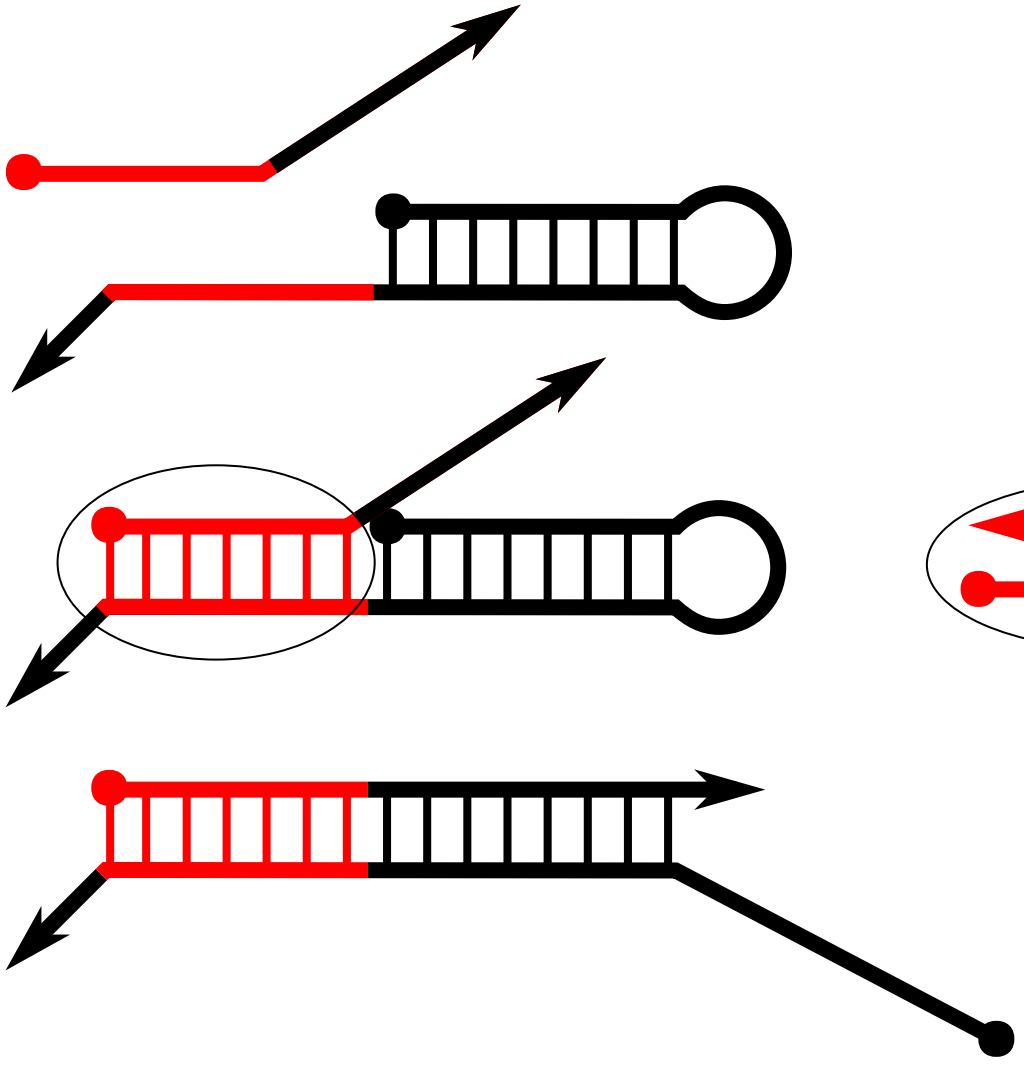


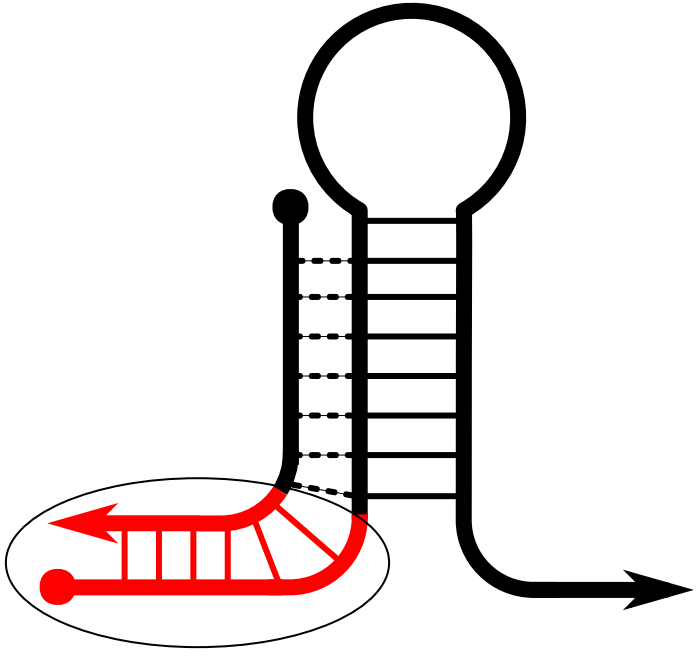
DESIGN SEQUENCE PAIRS





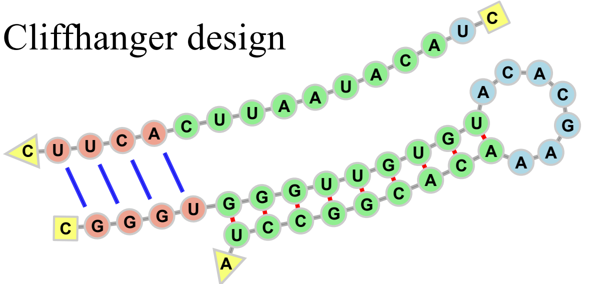
RNA-RNA INTERACTIONS





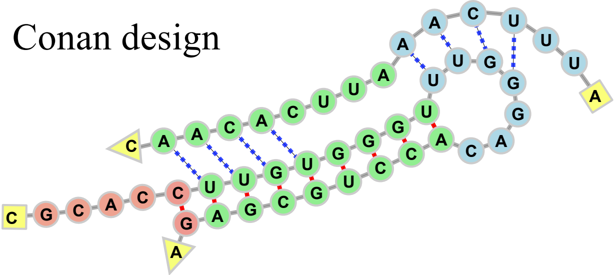
toehold
interactions

Cliffhanger design



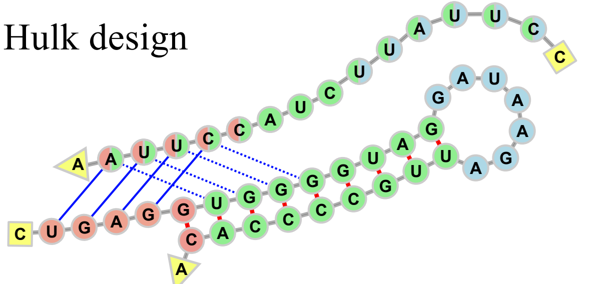
refolding using a toehold

Conan design

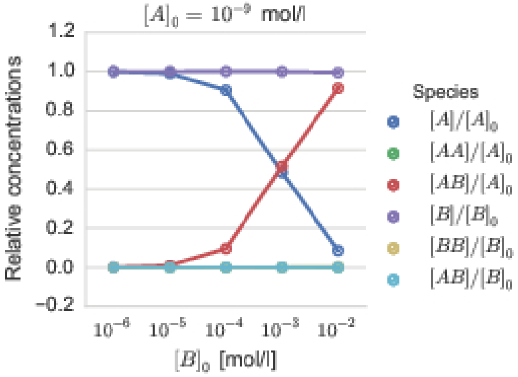


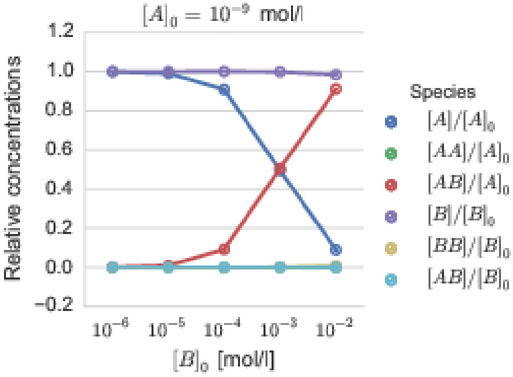
refolding without a toehold

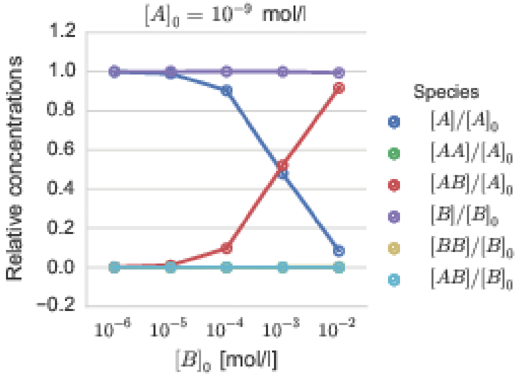
Hulk design

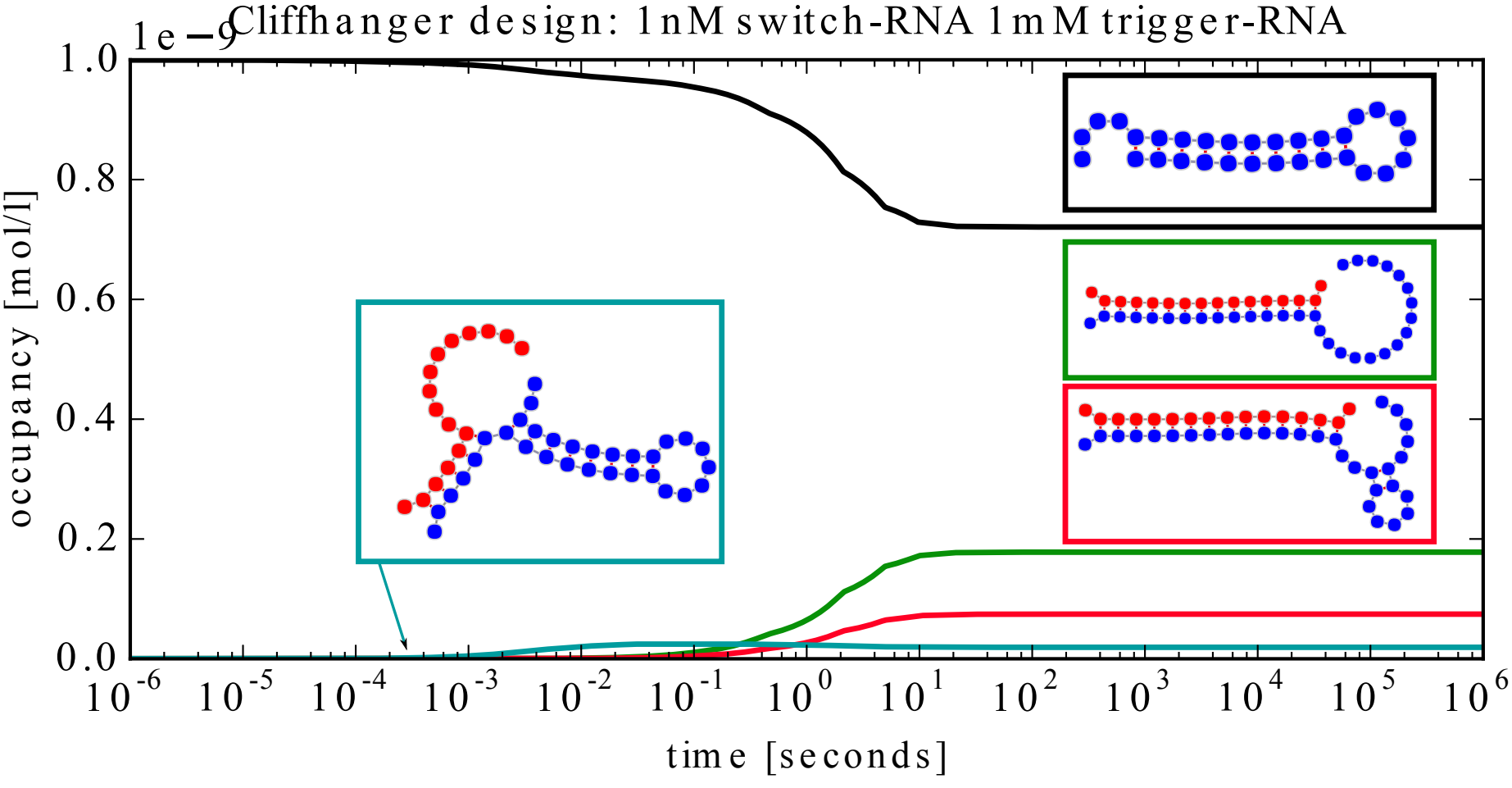


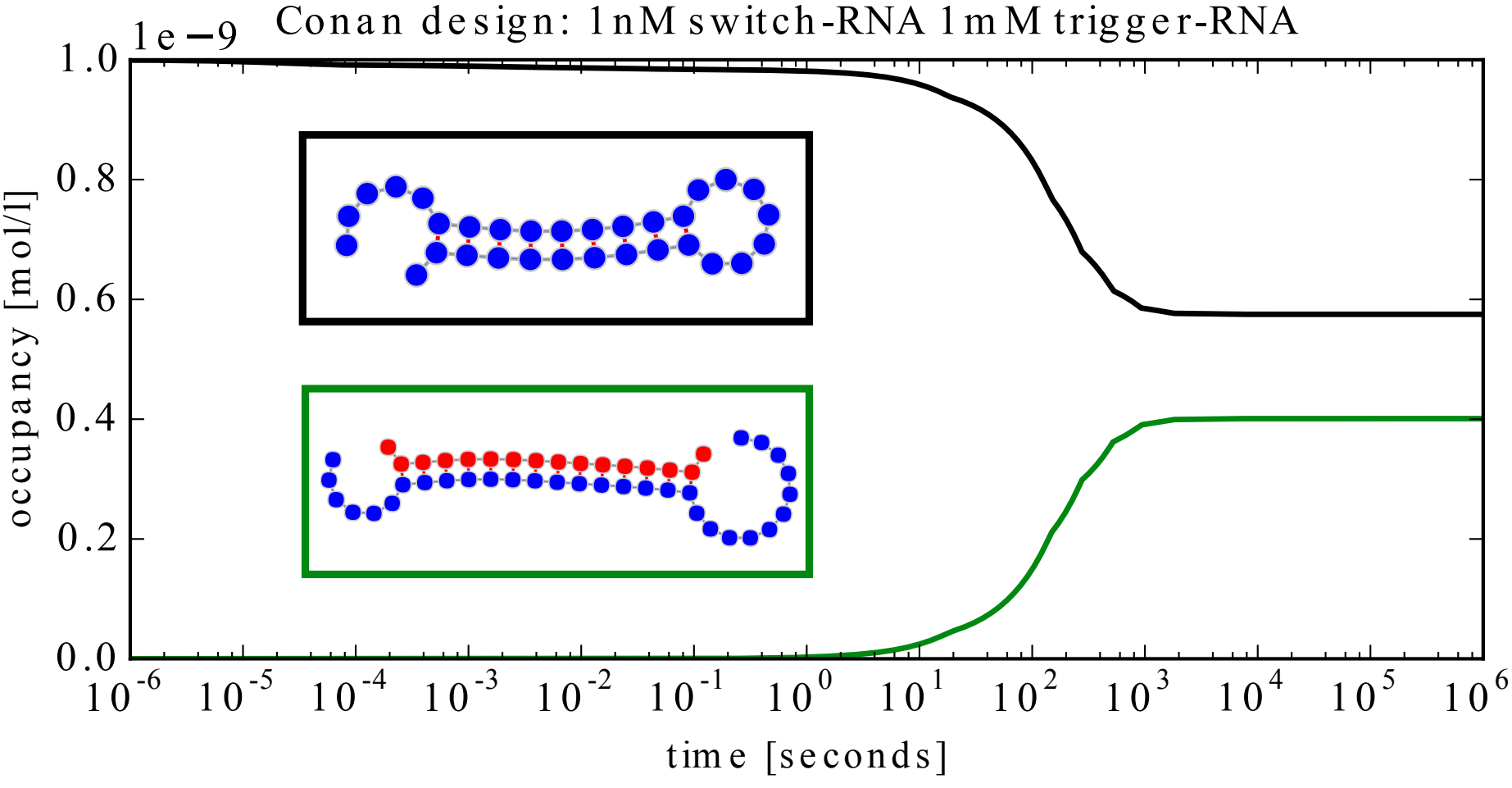
refolding with or without a toehold

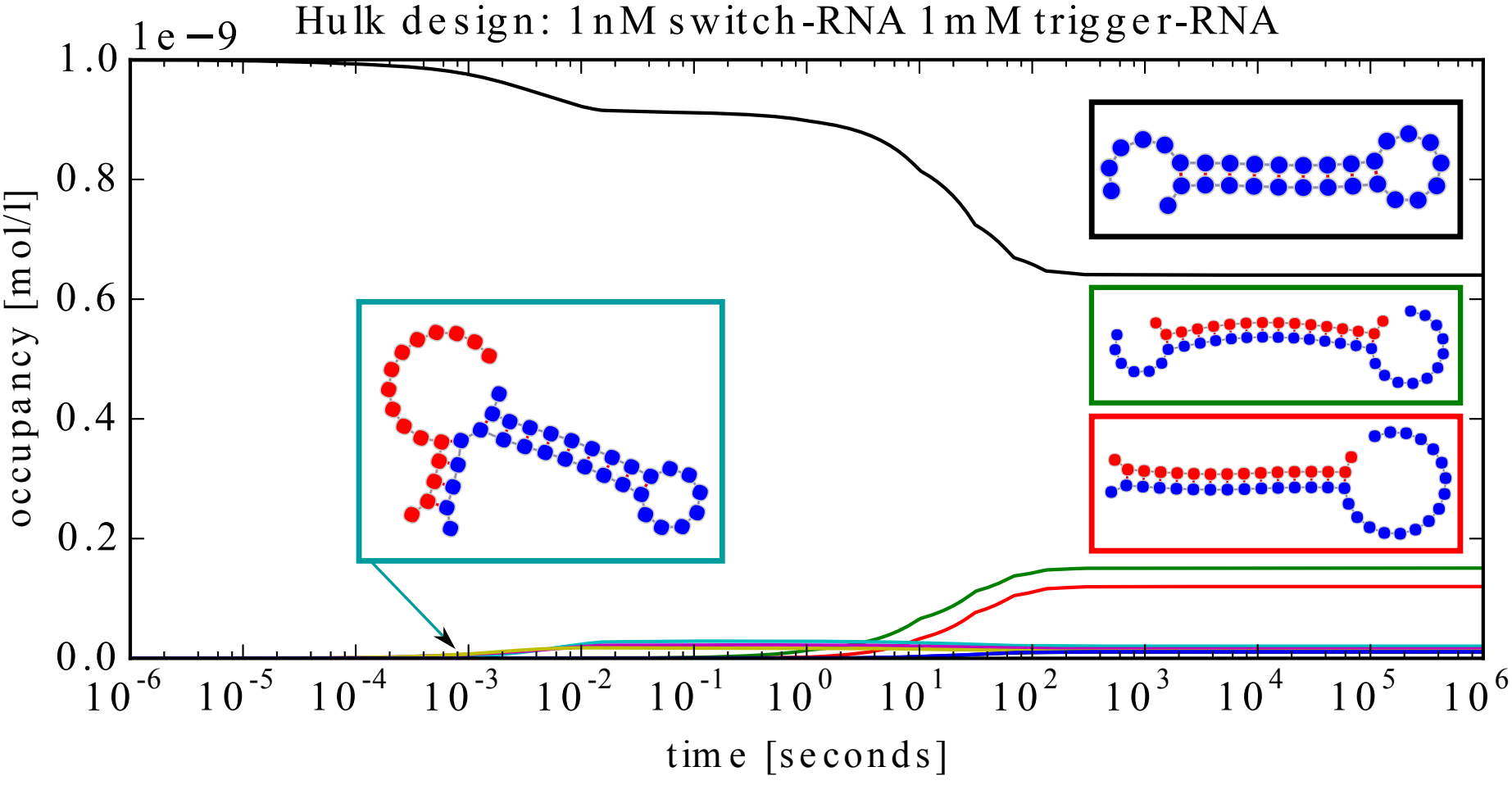


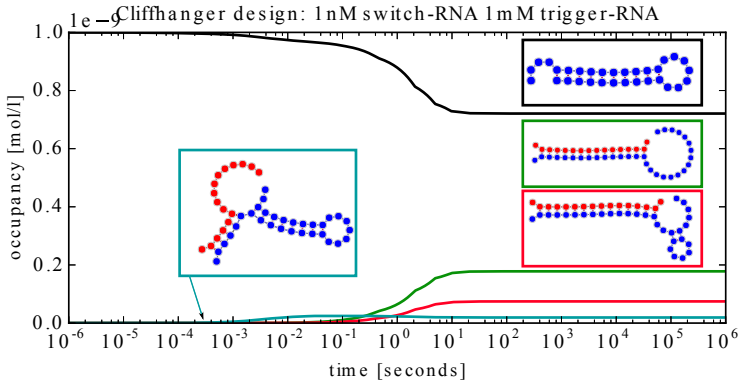


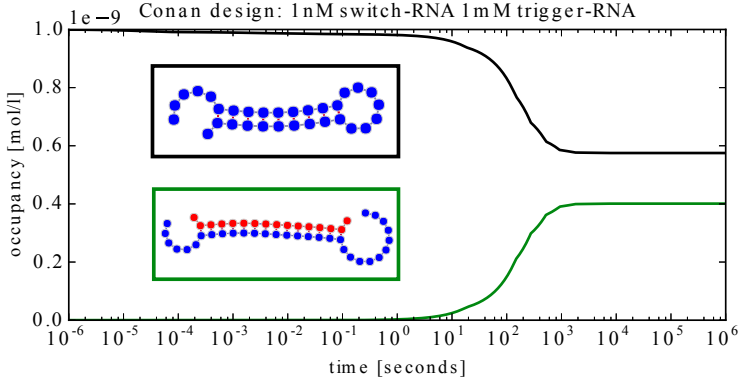


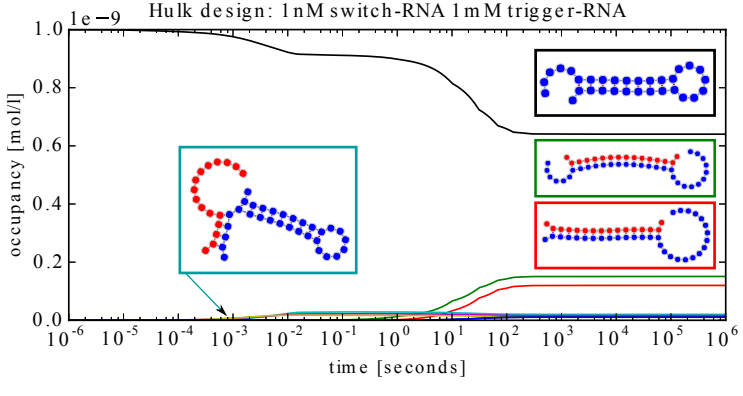

Cliffhanger design: 1nM switch-RNA 1mM trigger-RNA
1e−9
1.0
0.8
0.6
0.4
0.2
0.0
occupancy [mol/l]
10-6 10-5 10-4 10-3 10-2 10-1 100 101 102 103 104 105 106
time [seconds]

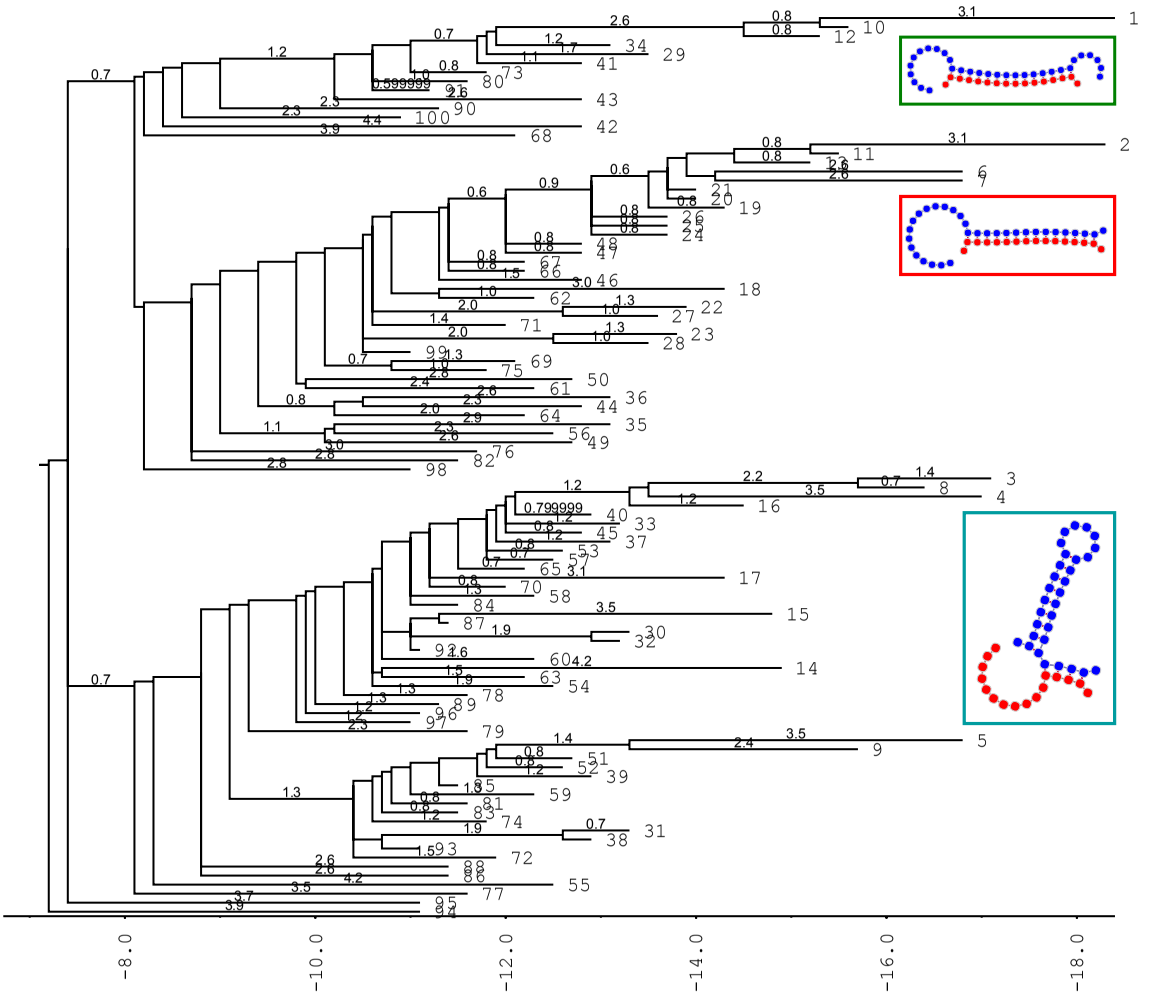

Conan design: 1nM switch-RNA 1mM trigger-RNA
1e−9
1.0
0.8
0.6
0.4
0.2
0.0
occupancy [mol/l]
10-6 10-5 10-4 10-3 10-2 10-1 100 101 102 103 104 105 106
time [seconds]


Hulk design: 1nM switch-RNA 1mM trigger-RNA
1e−9
1.0
0.8
0.6
0.4
0.2
0.0
occupancy [mol/l]
10-6 10-5 10-4 10-3 10-2 10-1 100 101 102 103 104 105 106
time [seconds]


Cliffhanger design: 1nM switch-RNA 1mM trigger-RNA
1e−9
occupancy [mol/l]
time [seconds]


Conan design: 1nM switch-RNA 1mM trigger-RNA
1e−9
occupancy [mol/l]
time [seconds]


Hulk design: 1nM switch-RNA 1mM trigger-RNA
1e−9
occupancy [mol/l]
time [seconds]


-8.0
-10.0
-12.0
-14.0
-16.0
-18.0

THANKS TO

Coworkers: Ivo L. Hofacker, Christoph Flamm

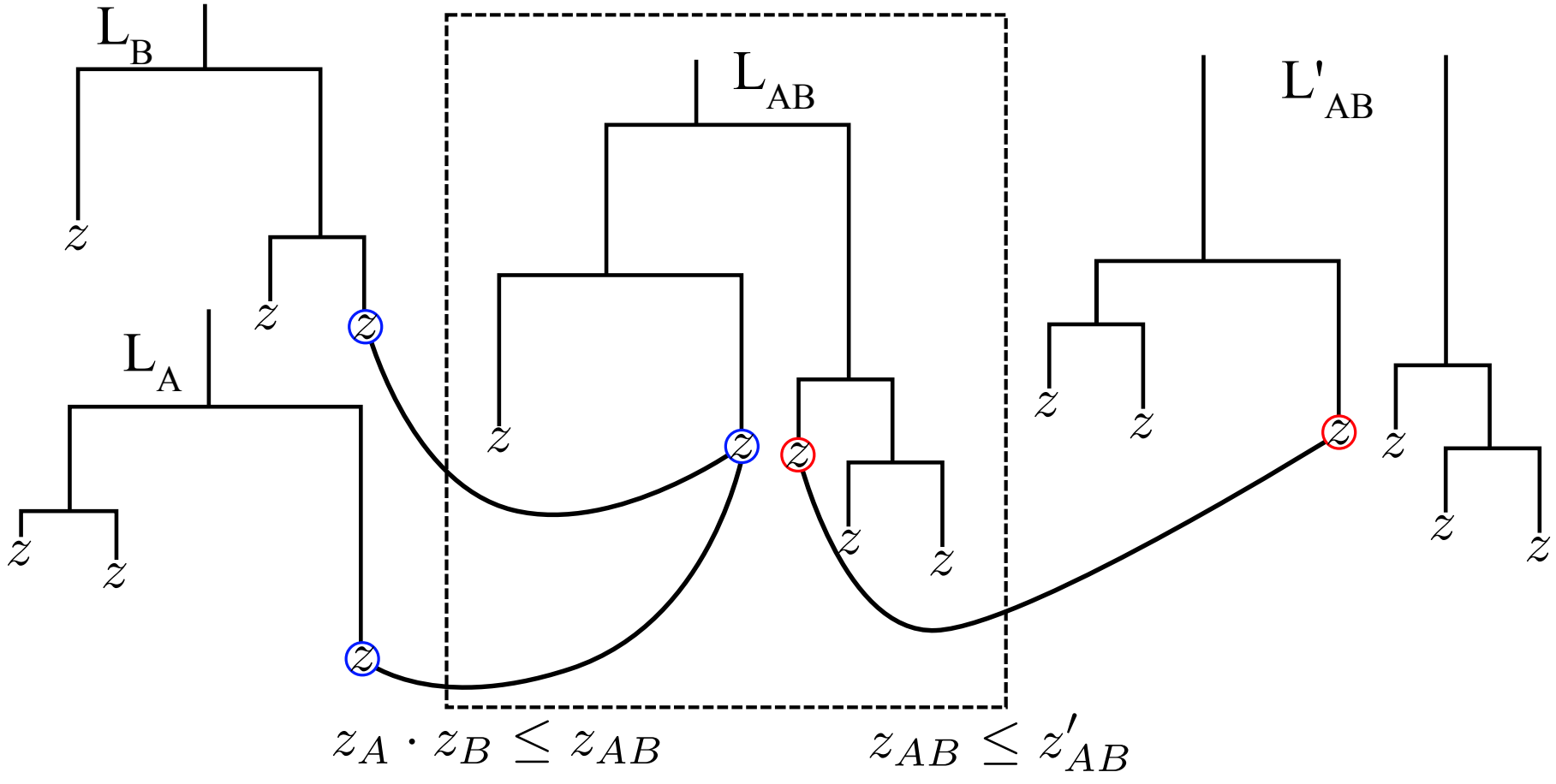
ViennaRNA package: Ronny Lorenz

Stefan Badelt, PhD Thesis, University of Vienna, (2016)
"Control of RNA function by conformational design."

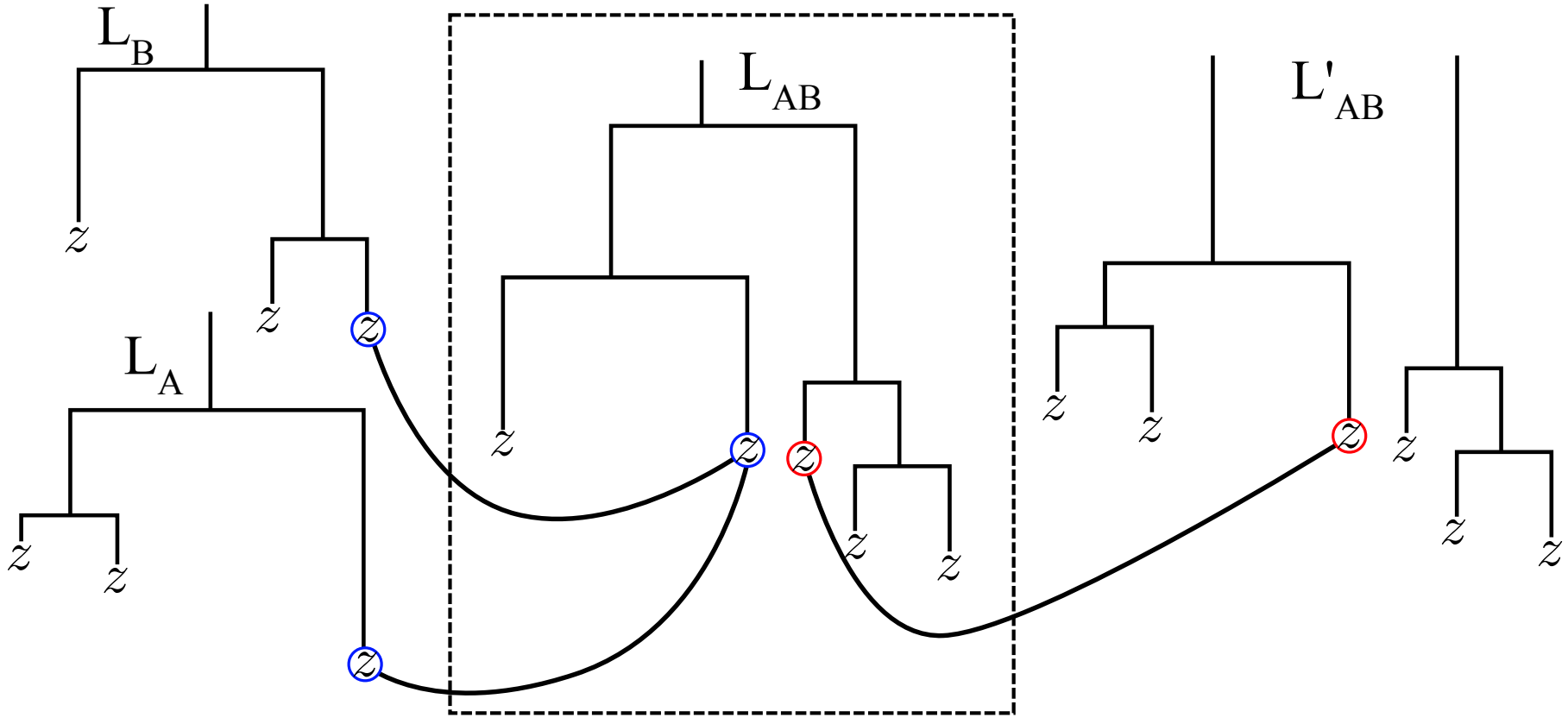
This research was funded in parts by the FWF International Programme I670, the DK RNA program FG748004 and the FWF project "SFB F43 RNA regulation of the transcriptome".

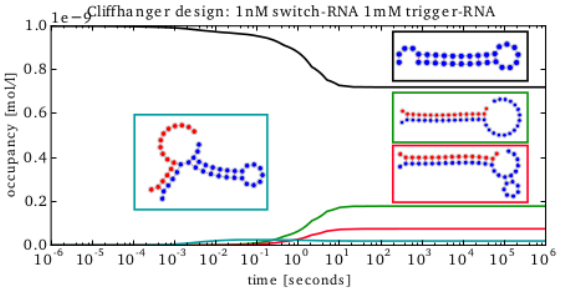
THE TBI

RNA-RNA INTERACTIONS

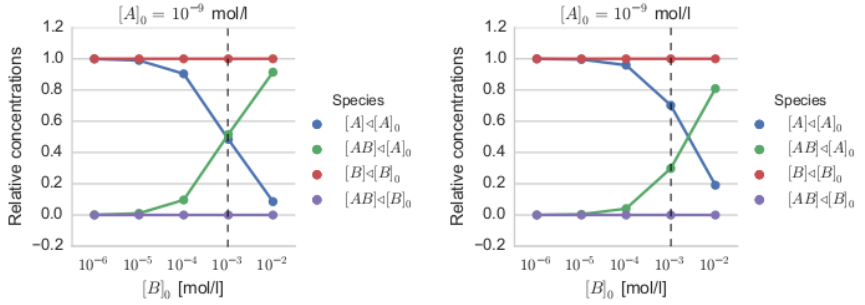


RNA-RNA INTERACTIONS

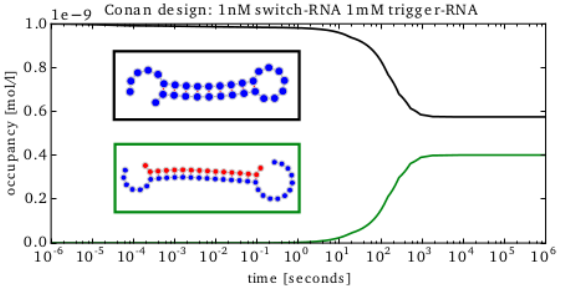




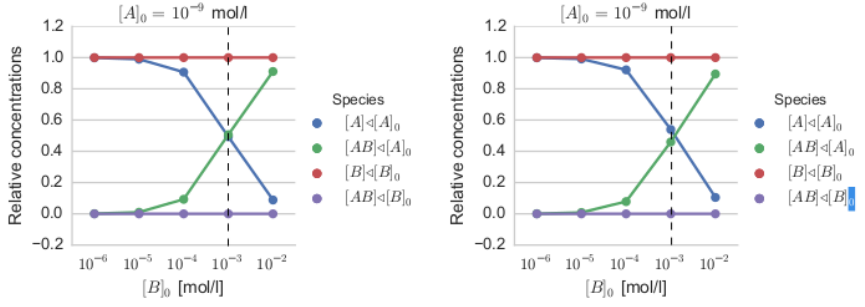
(a) Cliffhanger simulation



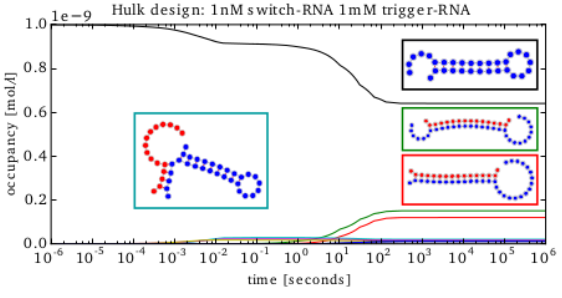
(b) Cliffhanger equilibrium



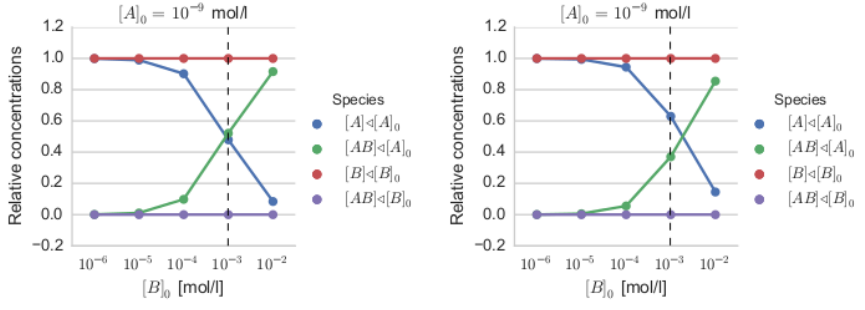
(c) Conan simulation



(d) Conan equilibrium



(e) Hulk simulation



(f) Hulk equilibrium